ادعيلي دعوة حلوة 💜

Whole endocrine pathology
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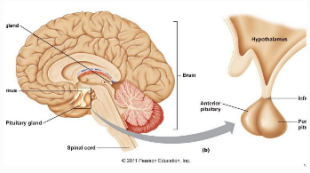
*هاد تجميع وترتيب للسلايدات، مو ملخّص.
*المعلومات اللي بالأحمر هي حمرا بالسلايدات.
*ارجعوا للصور من السلايدات من بداية محاضرة ٦.

Pituitary gland Diseases:

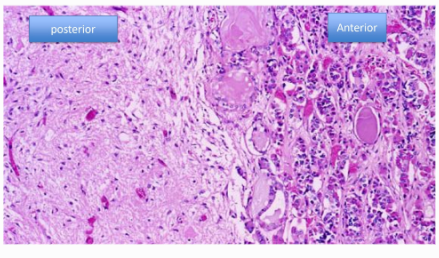
Endocrine system diseases | general principles

• **Mass effect = an enlargement of the gland which can compress adjacent structures.**
• Mass effect can be due to neoplastic or nonneoplastic conditions
• **Neoplastic include: adenoma & carcinoma**
• **Non neoplastic = hyperplasia**
- **End organ resistance = the gland is secreting the hormone but the target organ is not responding to it**. This occurs in some types of diabetes.



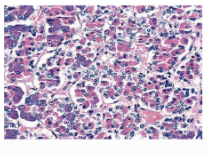
PITUITARY GLAND: THE ORCHISTRA MAESTRO
• The hormones secreted from the pituitary gland control levels of hormones secreted from all other endocrine glands.
Pituitary gland is a Small, bean shaped structure that lies at the base of the brain within the sella turcica.
- Sella turcica = pituitary fossa
• The sella turcica (Latin for Turkish seat) is a saddle-shaped depression in the body of sphenoid bone.
- The production of most pituitary hormones is controlled by positively and negatively acting factors from the hypothalamus which are carried to the anterior pituitary by a portal vascular system.
• The pituitary gland is composed of two morphologically & functionally distinct components: the anterior lobe (adenohypophysis) & the posterior lobe (neurohypophysis)
• **The anterior pituitary constitutes about 80% of the gland.**

	ANTERIOR PITUITARY	POSTERIOR PITUITARY
histology	Epithelial cells	Glial cells and neuronal axons
Embryological origin	Oral mucosa	Neural crest
Hormones secreted	TSH, PRL, ACTH, GH, FSH , LH.	ADH and oxytocin (*synthesized in hypothalamus but stored in posterior pituitary*)



• The anterior pituitary is composed of **epithelial cells** that secrete trophic hormones like: TSH, PRL, ACTH..

Anterior pituitary/ epithelial cells



- The posterior pituitary consists of **modified glial cells (pituicytes)** & axonal processes extending from the hypothalamus through the pituitary stalk to the posterior lobe (axon terminals).
- The posterior pituitary secretes: oxytocin & antidiuretic hormone (ADH, also called vasopressin).
- These **(oxytosin and ADH) are actually synthesized in the hypothalamus & stored within the axon terminals in the posterior pituitary.**

- Diseases of the anterior pituitary gland:

1. Mass effect

- Masses that can affect the pituitary: adenomas or carcinomas
- **Adenomas** can be 1) **secretory** (secrete one of the pituitary hormones) in this case the level of that hormone will increase = **hyperpituitarism**
- OR adenomas can be 2) **non secretory** so level of pituitary hormones unaffected = **normal hormonal levels**
- HOWEVER, if a non-secretory adenoma enlarges to the extent it **compresses** the surrounding normal pituitary tissue then level of hormone secretion from the normal tissue will be decreased resulting in **hypopituitarism**

• NOTE: pituitary carcinomas are rare & usually non-secretory.

- Mass effects of pituitary adenomas or cacinomas:

- Signs & symptoms:

1. Radiographic abnormalities of sella turcica:

a. sellar expansion.

b. bony erosions.

2. Compression of the optic chiasm (the X-shaped structure formed at the point below the brain where the two optic nerves cross over each other) results in visual field abnormalities.

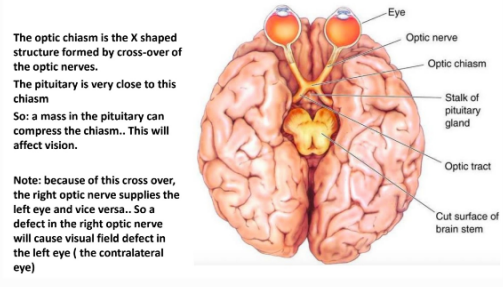
3. Elevated intracranial pressure: **headache, nausea, vomiting**.

- Note: any mass in the cranium (inside the skull) can cause increased intracranial pressure

4. seizures.

5. Cranial nerve palsies.

6. **pituitary apoplexy السكتة النخامية**



• **pituitary apoplexy** is an **Acute** hemorrhage into an **adenoma**, which causes **rapid enlargement** of the lesion. This will result in **decreased consciousness**.

• This is a ***neurosurgical emergency***.... Can cause sudden death.

• **Apoplexy = anger or rage.**

Pituitary adenomas:

• Functional or nonfunctional.

• **Functional = usually one cell type & one hormone produced.**

• Classified according to the hormones they produce into:

• Prolactinomas.. 20-30%.. The most common

• Null cell adenoma... 20%.. Non secretory

• ACTH cell adenoma.. 10-15%

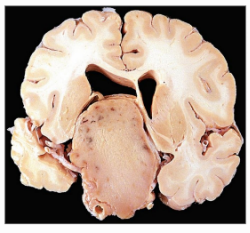
• TSH cell adenoma... 1%.. Least common

• pleurihormonal... 15%

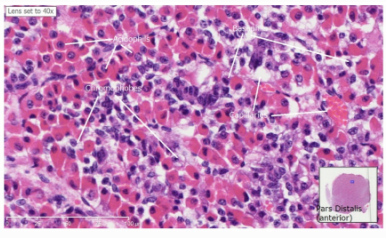
- Notes:

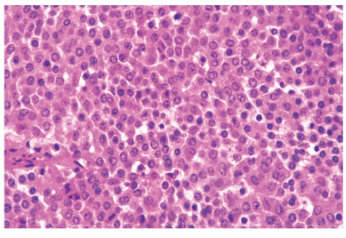
1. **TSH adenomas are rare**.. So if you have a patient with hyperthyroidism it will be very rare that the cause of his disease is related to the pituitary.
2. **pleuri-hormonal adenomas do exist**.. So a pituitary adenoma, although usually produces one hormone, it might secrete more than one type of hormones and patients will have

symptoms related to the hormones secreted.
• In clinical practice **10% of intracranial neoplasms are pituitary adenomas**.
• But **pituitary adenomas can be an incidental finding in 25% of autopsies**.
• **Peak: 4th to 6th decades**.
• Mostly single lesions = **solitary**
• Can be divided into micro & macro adenomas according to size.. Cutoff point: 1cm.



- Macroscopic appearance: Gross features of adenomas
- The usual adenoma is a **well-circumscribed**, lesion that if small, is confined by the sella turcica
- In 30% of cases, the adenomas are nonencapsulated & infiltrate adjacent bone, dura & brain.
- **Monomophic: one cell type.. All cells look similar**, whereas **in the normal pituitary several cell types exist.**





- Notes:
- Cellular monomorphism & the absence of a significant reticulin network distinguish pituitary adenomas from nonneoplastic anterior pituitary parenchyma
- The **functional status** of the adenoma cannot be reliably predicted from its **histologic appearance**.
- Adenomas that have TP53 mutations demonstrate brisk **mitotic activity** & are called **atypical adenomas to reinforce their potential for aggressive behavior.**

1.Prolactinomas = adenomas that produce prolactin= hyperprolactinemia

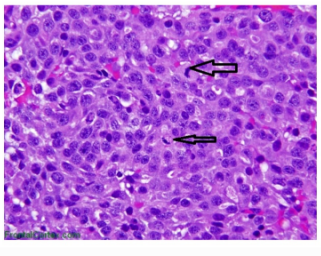
Hyperprolactinemia causes:

a. Amenorrhea & galactorrhea,

b. Loss of libido, & infertility

- prolactinomas usually are diagnosed at an earlier stage in women of **reproductive age** than in other persons .. Because they are more likely to have obvious symptoms

Atypical adenoma with increased mitosis..
These have TP53 mutation and are aggressive



- Other causes of hyperprolactinemia:

a. Pregnancy, & high-dose estrogen therapy,

b. Dopamine-inhibiting drugs (e.g., reserpine).

c. Any mass in the suprasellar compartment may disturb the normal inhibitory influence of hypothalamus on prolactin secretion, resulting in hyperprolactinemia, a mechanism known as **the stalk effect**.

2.Growth Hormone-Producing (Somatotroph) Adenomas
- Are **the second most common type of functioning pituitary adenoma**
- May be quite large at time of diagnosis because the clinical manifestations of excessive growth hormone may be subtle,

- clinical manifestations:

Increased growth hormone can cause Gigantism or acromegaly:

If a GH-secreting adenoma occurs before the epiphyses closes (in children) it causes gigantism.

- Gigantism: generalized increase in body size, with disproportionately long arms & legs.
- Acromegaly: If elevated levels of growth hormone persist, or develop After closure of the epiphyses, affected persons develop acromegaly, in which:

1. Growth is most conspicuous in soft tissues, skin, & viscera & in face bones, hands, & feet
2. Enlargement of the jaw results in its protrusion with separation of the teeth.
3. Enlarged hands & feet with broad, sausage-like fingers

3.Corticotroph cell adenomas

- May be:

1. Clinically silent
2. May cause hypercortisolism = increased cortisol = **Cushing syndrome**

-Large, clinically aggressive corticotroph cell adenomas may develop **after surgical removal of the adrenal glands** for treatment of Cushing syndrome, this condition is **Nelson syndrome,** because of the metabolic demands & the loss of the feedback mechanism.

***Because ACTH is synthesized as part of a larger prohormone substance that includes melanocytestimulating hormone (MSH), hyperpigmentation may be a feature.**

4.Gonadotroph LH-producing & FSH adenomas

- Can be **difficult to recognize**, because they secrete hormones inefficiently, & the secretory products usually do not cause a recognizable clinical syndrome.

Pituitary carcinomas:

- are exceedingly rare & in addition to **local extension beyond the sella turcica**, these tumors virtually **always demonstrate distant metastases**.

- As a general rule: Most endocrine carcinomas are diagnosed depending on *behavior* (presence of metastases) & *not on histological appearance*. i:e under the microscope adenoma & carcinoma can look similar.. You need to know the clinical information & check if the patient has metastatic disease in order to call the lesion carcinoma.

- Second type of disease that affect the pituitary **other than mass effect** is

2. hormonal over or under production:

1) Hyperpituitarism

• MOST COMMON CAUSE: functional adenoma.

• Other causes: 1. Hyperplasia 2. Carcinoma 3. Secretion of pituitary hormones by nonpituitary tumors 4. Hypothalamic disorders.

2) Hypopituitarism:

Occurs if there is Loss of at least 75% of anterior pituitary

- Causes:

a. Congenital absence (exceedingly rare)

b. Hypothalamic tumors, associated with posterior pituitary dysfunction.

c . Non-functioning pituitary adenomas .. Most common/ occurs when the adenoma compresses normal pituitary tissue & affects its function.

d. Ischemic necrosis of the anterior pituitary, e;g Sheehan syndrome

e. Ablation of the pituitary by surgery or irradiation

f. Inflammatory lesions such as sarcoidosis or tuberculosis
g. Trauma & Metastatic neoplasms involving the pituitary

Sheehan syndrome, or postpartum necrosis of anterior pituitary, is the most common form of clinically significant ischemic necrosis of the anterior pituitary.

- During pregnancy, the anterior pituitary enlarges considerably, because of an increase in the size & number of prolactin-secreting cells & this physiologic enlargement is not accompanied by an increase in blood supply from the low-pressure portal venous system.
- The enlarged gland is thus vulnerable to ischemic injury, especially in women who experience significant hemorrhage & hypotension during the postpartum period.
- Note: Sheehan syndrome is named after a British pathologist who described the condition.

- POSTERIOR PITUITARY SYNDROMES:

- Impairment of oxytocin synthesis & release has not been associated with significant clinical abnormalities.
- The clinically important posterior pituitary syndromes involve ADH = vasopressin

ADH deficiency: causes diabetes insipidus (DI) characterized by **excessive urination (polyuria)** caused by an inability of the kidney to properly resorb water from the urine
SO: **patients are thirsty & have polydipsia = excessive drinking**

- Diabetes insipidus can result from several causes:

a. Head trauma, Neoplasms.
b. Inflammatory disorders & surgical procedures of the hypothalamus & pituitary.
c. May be idiopathic.

- Note:- Diabetes insipidus from ADH deficiency is designated as **central DI** , to differentiate it from nephrogenic DI.

- The clinical manifestations of DI include:

a. The excretion of large volumes of **dilute** urine with an inappropriately **low specific gravity**
b. **Serum sodium & osmolality are increased as a result of excessive renal loss of free water resulting in thirst & polydipsia**

- Patients who can drink water generally can compensate for urinary losses; patients who are bedridden, or are limited in their ability to obtain water may develop life threatening dehydration.

Lec3: Thyroid diseases:

Increased thyroid hormone (T3 & T4) = thyrotoxicosis

*Thyrotoxicosis means: increased thyroid hormone, regardless of the cause of the increase.

***Hyperthyroidism is the most common cause of thyrotoxicosis** & it means there is actual increase in thyroid hormone **production** from the thyroid gland.

NOTE: 1. actual increase excludes relative increase in cases of thyroiditis where there is **destruction** of the gland causing increased **release** (not production) of thyroid hormone, so there is a relative net increase in T3 & T4 ➡️ **thyrotoxicosis but no hyperthyroidism**

A. Thyrotoxicosis Associated with hyperthyroidism (Thyroid hyperfunction):

1. **Primary**

a. Diffuse toxic **hyperplasia** (Graves disease)

b. **Hyperfunctioning** (Toxic) multinodular goitre.

c. **Hyperfunctioning** (toxic) adenoma

2. **Secondary** -- TSH-secreting pituitary adenoma (rare)

B. Thyrotoxicosis not associated with hyperthyroidism : less common

- Excessive release of pre-formed hormones in thyroiditis (just increased release with no increased overall production)

- Clinical manifestations of thyrotoxicosis:

• Thyroid hormones increase basal metabolic rate, increase appetite, increase breakdown of fat and glucose

• Also increase heart rate, cause hypertension

• Increase body temperature

• SO if these hormones are increased you expect to see a wide range of symptoms.

a. Constitutional symptoms : **warm flushed skin**, **heat intolerance & excessive sweating**, **weight loss** despite increased appetite.

b. **Malabsorption, & diarrhoea** (because of ⬆️ intestinal motility)

c. **Tachycardia & heart failure** in elderly patients due to aggravationتفاقم of pre-existing heart disease

d. **Nervousness, tremor, & irritability**.

e. A **wide, staring gaze & lid lag** because of sympathetic overstimulation of the levator palpebrae superioris

f. 50% develop proximal muscle weakness (**thyroid myopathy**).

- Lab tests:

• The measurement of **serum TSH is the most useful single screening test** for hyperthyroidism, because TSH levels are decreased even at the earliest stages, when the disease may still be subclinical

- Once the diagnosis of thyrotoxicosis has been confirmed, measurement of **radioactive iodine** uptake by the thyroid gland is valuable in determining the **etiology**.

For example, such scans may show:

a. Diffusely increased (whole-gland) uptake in **Graves disease**,

b. Increased uptake in a solitary nodule in **toxic adenoma**.

c. Or decreased uptake in **thyroiditis**.

II.HYPOTHYROIDISM

This disorder may be divided into **a. primary** and **b. secondary** categories, depending on whether it arises from **a. an intrinsic abnormality** in the thyroid or **b. hypothalamic or pituitary disease**

1. Primary hypothyroidism causes أسبابه:

a. congenital b. autoimmune c. iatrogenic

1. genetic defect perturb thyroid development (thyroid dysgenesis) or the synthesis of thyroid hormone (dyshormonogenetic goiter) are rare overall

2. Endemic deficiency of dietary iodine is typically manifested by hypothryoidism early in childhood & has been also called congenital

- It is a common cause of hypothyroidism in infants and children worldwide

3. Autoimmune thyroid disease is a common cause of hypothyroidism in regions of the world where iodine is supplemented in dietary salt products.

-The vast majority of cases of autoimmune hypothyroidism are due to Hashimoto thyroiditis

4. Iatrogenic hypothyroidism can be caused by either surgical or radiation-induced ablation of thyroid parenchyma, or as an unintended adverse effect of certain drugs

• **The clinical manifestations of hypothyroidism include cretinism and myxedema**

1. Cretinism

- A. Endemic cretinism is **caused by iodine deficiency** is now much less frequent because of the supplementation of salt with iodine.
- B. By contrast, **enzyme defects** that interfere with thyroid hormone synthesis are a **cause of** sporadic cretinism

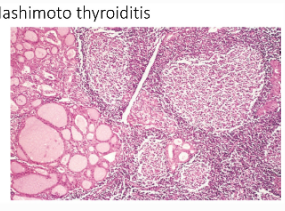
• Clinical features of cretinism:

1) impaired development of the a. skeletal system & b. central nervous system,
2) severe mental retardation, short stature, coarse facial features, a protruding tongue, & umbilical hernia

2.Myxedema - Hypothyroidism in older children & adults

- The initial symptoms include generalized fatigue, apathy, & mental sluggishness,
- Decreased sympathetic activity results in constipation & decreased sweating.
- The skin is cool & pale because of decreased blood flow.,

III.Thyroiditis



1.Chronic Lymphocytic (Hashimoto) Thyroiditis

• Hashimoto thyroiditis is **the most common cause of hypothyroidism** in areas of the world where iodine levels are sufficient.

- It is characterized by gradual thyroid failure secondary to autoimmune destruction of the thyroid gland.
- It is most prevalent between 45 and 65 years of age & is more common in women.
- Although it is primarily a disease of old women, it can occur at any age, including childhood.

- MORPHOLOGY:

- The thyroid usually is diffusely & symmetrically enlarged.
- Microscopically:

a. widespread infiltration of the parenchyma by a mononuclear inflammatory infiltrate

containing small lymphocytes, plasma cells, & well-developed germinal centers.
b. The thyroid follicles are
1.atrophic 2.lined by epithelial cells distinguished by the presence of abundant eosinophilic, granular cytoplasm, termed **Hürthle**, or **oxyphil**, cells.

- Clinical manifestation:

• **Painless enlargement** of the thyroid, usually associated with some degree of **hypothyroidism**.
- The enlargement of the gland usually is **symmetric & diffuse**,
- In the usual clinical course, hypothyroidism develops gradually
- In some cases **it may be preceded by transient thyrotoxicosis** caused by disruption of thyroid follicles,
- with secondary release of thyroid hormones called **Hashitoxicosis** & during this phase, **free T4 & T3 concentrations are elevated, TSH is diminished, & radioactive iodine uptake is decreased**.
- As hypothyroidism supervenes, T4 & T3 levels progressively fall, accompanied by a compensatory increase in TSH.
a. Patients with Hashimoto thyroiditis often have other autoimmune diseases
b. Are at increased risk for the development o B-cell non-Hdgkin Lymphomas which typically arise within the thyroid gland.
c. The relationship between Hashimoto disease and thyroid epithelial cancers remains controversial, with some morphologic and molecular studies suggesting a predisposition to papillary carcinomas.

2. Subacute Granulomatous (de Quervain) Thyroiditis

De-Quervain thyroiditis-granuloma

- Is much less common than Hashimoto disease.
- Is most common between 30 and 50 years of age
- Occurs more frequently in women than in men.
- Is believed to be caused by a viral infection, and not by an autoimmune process.
- A majority of patients have a history of an upper-respiratory infection shortly before the onset of thyroiditis
- The process spontaneously remits.

• MORPHOLOGY:

- The gland is has an **intact capsule**.
- Histologic examination reveals **disruption of thyroid follicles**, **extravasation of colloid**, and **infiltrating neutrophils**, which are replaced over time by lymphocytes, plasma cells, and macrophages.
- The extravasated colloid provokes an exuberant granulomatous reaction with giant cells, some containing fragments of colloid.

- Clinical Features:

- The onset often is acute.
- It is characterized by neck pain (particularly with swallowing), fever, malaise, and variable enlargement of the thyroid.
- Transient Thyrotoxicosis may occur, as a result of disruption of thyroid follicles and release of excessive thyroid hormone.
- The **leukocyte count and erythrocyte sedimentation rates are increased**.

- With progression of the gland **destruction**, a **transient hypothyroid phase** may ensue.
- The condition typically is **self-limited**, with most patients returning to a euthyroid state within 6 to 8 weeks

3. Subacute Lymphocytic Thyroiditis

- Also is known as **silent or painless thyroiditis**;
- In a subset of patients, the onset follows pregnancy (**postpartum thyroiditis**)
- This disease is most likely autoimmune in etiology, as circulating antithyroid antibodies are found in a majority of patients.
- The patients present with a **painless neck mass** or features of **thyroid hormone excess**.
- The initial phase of thyrotoxicosis is followed by return to a euthyroid state within a few months.
- *In a minority of affected individuals, the condition eventually progresses to* ***hypothyroidism***

4. Riedel thyroiditis

- Is characterized by extensive **fibrosis** involving the thyroid & contiguous neck structures.
- Clinical evaluation demonstrates a **hard & fixed thyroid mass**, **simulating a thyroid neoplasm**.
- It may be associated with **idiopathic fibrosis in other sites in the body, such as the retroperitoneum**.

Riedel thyroiditis

IV .Graves Disease:

- Is **the most common cause of endogenous hyperthyroidism**.
- It is characterized by a **triad:**

1. **Thyrotoxicosis**, caused by a diffusely enlarged, hyperfunctional thyroid present in all cases
2. An infiltrative ophthalmopathy with resultant **exophthalmos**, in about 40% of patients.
3. A localized, **infiltrative dermopathy** (sometimes designated **pretibial myxedema**), in a minority of cases.

- Graves disease has a peak incidence between 20 and 40 years of age, with **women** being affected up to seven times more commonly than men.

- Pathogenesis:

- Many manifestations of Graves disease are caused by **autoantibodies** to TSH

1. Thyroid stimulating immunoglobulin

- **This IgG ab binds to the TSH receptor & mimics TSH action, causing ⬆️ release of T3 & T4.**
- Almost all individuals with Graves disease have detectable amounts of this autoantibody, which is relatively **specific for** Graves disease.

2. Thyroid growth stimulating immunoglobulin

- Directed against the TSH receptor, these antibodies have been implicated in the **proliferation of thyroid follicular epithelium**.

3. TSH binding inhibitor immunoglobulin

- These anti-TSH receptor antibodies prevent TSH from binding to its receptor on thyroid epithelial cells and in so doing may **inhibit thyroid cell function**.

- Pathogenesis of infiltrative ophthalmopathy:

• There is ⬆️ **in the volume of retro-orbital connective tissue & extraocular muscles** due to:
(1) marked **infiltration of the retro-orbital space** by mononuclear cells, predominantly T cells;
(2) Inflammatory **edema & swelling** of extraocular muscles;

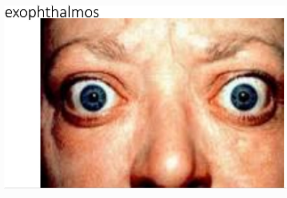
(3) Accumulation of **glycosaminoglycans** such as hyaluronic acid & chondroitin sulfate;
(4) **Increased adipocytes No.** (fatty infiltration).
• These changes displace the eyeball forward, potentially interfering with the function of the extraocular muscles.

- MORPHOLOGY:

- In the typical case of Graves disease, the thyroid gland is enlarged (usually **symmetrically**) due to diffuse **hypertrophy & hyperplasia** of thyroid follicular epithelial cells.
- On microscopic examination, the follicular epithelial cells in untreated cases are tall, columnar, & more crowded than usual.
- **Lymphoid infiltrates** is present throughout the interstitium.

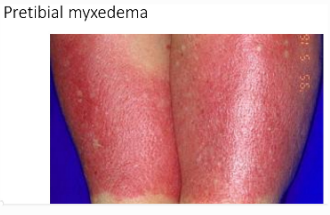
clinical manifestations:

- Include those common to all forms of thyrotoxicosis,
- And those associated uniquely with Graves disease: **ophthalmopathy** is specific to Graves disease & not present in other causes of exophthalmos.
- **Sympathetic overactivity** produces a characteristic wide, staring gaze & lid lag. Which are not specific to Graves disease


exophthalmos

- The ophthalmopathy of Graves disease results in abnormal protrusion of the Eyeball (exophthalmos)
- The exophthalmos may persist or progress despite successful treatment of the thyrotoxicosis, sometimes resulting in **corneal injury**.
- **The infiltrative dermopathy most commonly involves the skin overlying the shins, where it manifests as scaly thickening & induration of skin** (pretibial myxedema).

- Laboratory findings in Graves disease:


Pretibial myxedema

a. **Elevated serum free T4 and T3 & depressed serum TSH**.
b. **Radioactive iodine uptake is increased** diffusely because of ongoing stimulation of the thyroid follicles by TSIs (immunoglobulins).

V. DIFFUSE AND MULTINODULAR GOITER:

- Enlargement of the thyroid, or goiter, **is the most common manifestation of thyroid disease**.
- Diffuse & multinodular goiters are the result of **impaired synthesis of thyroid hormones** most often caused by **Dietary iodine deficiency**.
- **Impairment of thyroid hormone synthesis** leads to a compensatory **rise in the serum TSH**, which drives the **hypertrophy & hyperplasia** of thyroid follicular cells &, ultimately, enlargement of the thyroid gland.
- These compensatory changes overcome the hormone deficiency & maintain an **euthyroid metabolic state** in the vast majority of affected individuals.
- If the underlying disorder is **severe** (e.g., a *congenital* biosynthetic defect), the compensatory responses may be inadequate, resulting in **goiterous hypothyroidism.**

- Pathogenesis:

- Goiters can be **endemic** or **sporadic**.

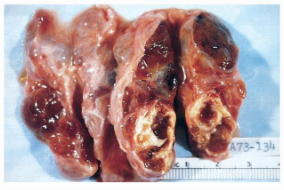
1. **Endemic goiter** occurs in geographic areas where the diet contains little iodine.

- Endemic = when goiters are present in >10% of the population in a given region.
- Common in mountainous areas of the world, including the Himalayas & the Andes.
- With increased availability of dietary iodine supplementation, the frequency & severity of endemic goiter have declined significantly.

2. Sporadic goiter

- Occurs less frequently than endemic goiter.
- More common in **females** than in males, with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T4.
- Sporadic goiter may be caused by several conditions, including:

a. **Excessive ingestion** of substances that interfere with T3 & T4 synthesis, such as calcium & vegetables such as cabbageملفوف, caulifowerقرنبيط.



b. inherited **enzymatic defects** that interfere with T3 & T4 synthesis **(dyshormonogenetic goiter).**

- Note: In most cases, the cause of sporadic goiter is not apparent.

- Clinical Features:

-The dominant clinical features of goiter are those caused by the **mass effects** of the enlarged gland causing:

a. **cosmetic problem** of a large neck mass

b. Goiters also may cause **airway obstruction, dysphagia, & compression** of large vessels in the neck and upper thorax (so-called **superior vena cava syndrome**).

- Note: Multinodular goiters typically are hormonally silent.

- A a minority (approximately 10% over 10 years) manifest with **thyrotoxicosis** secondary to the development of **autonomous nodules** that produce thyroid hormone **independent of TSH stimulation**.
- This condition, known as **toxic multinodular goiter** or **Plummer syndrome**, is not accompanied by the infiltrative ophthalmopathy & dermopathy of Graves disease–associated thyrotoxicosis.
- The incidence of malignancy in long-standing multinodular goiters is low, (<5%) but not zero, & concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (e.g., **hoarseness**)

VI.THYROID NEOPLASMS:

- From a clinical standpoint, the **possibility of a tumor is of major concern in patients with thyroid nodules**.
- Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be either:

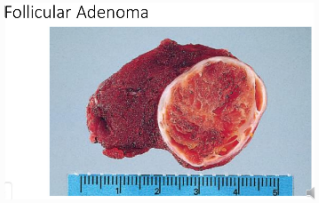
a. **benign adenomas**.

b. **Localized, non-neoplastic conditions** (e.g., a dominant nodule in multinodular goiter, simple cysts, or foci of thyroiditis).

- **Carcinomas of the thyroid, are uncommon**, accounting for <1% of solitary thyroid nodules.
- Several clinical criteria provide a clue to the nature of a given thyroid nodule:

1. **Solitary nodules**, in general, are more likely to be **neoplastic** than are multiple nodules.
2. Nodules in very young**<20 years** or vey old **>70 years** individuals are more likely **neoplastic**.
3. Nodules in **males** are more likely to be **neoplastic** than are those in females.
4. A **history of radiation** exposure is associated with ⬆️ incidence of thyroid **malignancy**.
5. Nodules that take up radioactive iodine in imaging studies (**hot nodules**) are more likely to be **benign**.

Follicular Adenomas



- Are **benign neoplasms** derived from follicular epithelium.
- Usually **solitary**.
- On clinical & morphologic grounds, they may be **difficult to distinguish** from a dominant **nodule in multinodular goiter**, or from less common **follicular carcinomas**.
- Although the vast majority of adenomas are **nonfunctional**, a small proportion produce thyroid hormones called **toxic adenomas**, causing clinically apparent **thyrotoxicosis**

Thyroid Carcinomas

- A **female** predominance has been noted among patients who develop thyroid carcinoma **in the early & middle adult years**.
- By contrast, cases seen in **childhood & late adulthood are distributed equally between males & females**.
- Most thyroid carcinomas (except medullary carcinomas) are derived from the thyroid follicular epithelium.
- Subtypes of thyroid carcinomas:

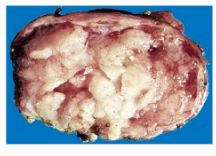
a. **Papillary** carcinoma (accounting for >85% of cases)
b. **Follicular** carcinoma (5% to 15% of cases)
c. **Anaplastic** (undifferentiated carcinoma (<5% of cases))
d. **Medullary** carcinoma (5% of cases)

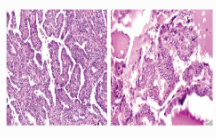
- Environmental Factors:

1. The major risk factors predisposing to thyroid cancer is **exposure to ionizing radiation** particularly during the first 2 decades of life.
- There was a marked increase in the incidence of papillary carcinomas among children exposed to radiation as treatment for malignant tumors such as lymphomas.
2. Deficiency of **dietary iodine** (and by extension, an association with **goiter**) is linked with a higher Frequency of follicular carcinomas

I. Papillary Carcinoma

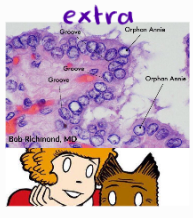
- **The most common form of thyroid cancer**.
- They may **occur at any age.**
- They **account for the vast majority of thyroid carcinomas associated with previous exposure to ionizing radiation**.





- MORPHOLOGY:
- Papillary carcinomas are **solitary or multifocal** lesions.
- Some tumors may be well circumscribed & encapsulated.
- others infiltrate the adjacent parenchyma.
- The microscopic hallmarks of papillary neoplasms:

a. **Branching** papillae having a **fibrovascular stalks** covered by a single to multiple layers of **cuboidal** epithelial cells



b. **Nuclei are optically clear** imparts تعطي empty appearance called **groundglass** or **Orphan Annie eye** nuclei.
c. Intranuclear inclusions (“**pseudo-inclusions**”)
d. Intranuclear **grooves**

- **Note:** These nuclear features are sufficient for the diagnosis of papillary carcinoma, even

in the absence of papillary architecture. .

e. Concentrically **calcified structures** termed **psammoma bodies.**

f. Foci of lymphatic invasion by tumor are often present, but **involvement of blood vessels is relatively uncommon**.

- **Metastases to adjacent cervical lymph nodes** occur in one-half of cases.

- Clinical Features:

- Papillary carcinomas are **nonfunctional** tumors.

- Manifest most often as a **painless mass** in the neck, either within the thyroid or as a metastasis in a cervical lymph nodes.

- Are indolent lesions, with 10-year survival rates in excess of 95%.

- The presence of **isolated cervical node metastases does not have a significant influence on prognosis**.

- In a minority of patients, **hematogenous metastases** are present at the time of diagnosis, most commonly to the **lung**.

- The long-term survival of patients with papillary thyroid cancer is dependent on several factors, including:

a. **age** (the prognosis is less favorable among patients >40 years of age),

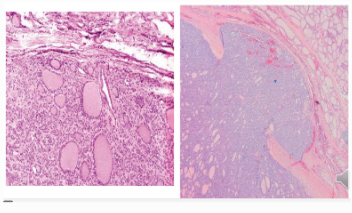
b. presence of **extrathyroidal extension**,

c. presence of **distant metastases** (stage).

2. Follicular Carcinoma

- It account for 5% to 15% of primary thyroid cancers.

- They are more common in **women** (occurring in a ratio of 3:1) & **manifest at an older age than papillary carcinomas**.



- The a peak incidence between 40 & 60 years of age.

- Is more frequent in areas with **dietary iodine deficiency** (accounting for 25%–40% of thyroid cancers)

- Morphology:

- On microscopic examination, most follicular carcinomas are composed of uniform cells forming small follicles, **similar to normal thyroid.**

- Follicular carcinomas may be:

a. **widely invasive**, infiltrating the thyroid parenchyma & extrathyroidal soft tissues.

b. **minimally invasive** type which are sharply demarcated lesions that may be impossible to distinguish from follicular adenomas on gross examination.

- Clinical Features:

- Follicular carcinomas manifest as **solitary cold thyroid nodules**

- In rare cases, they may be **hyperfunctional.**

- Tend to metastasize through the bloodstream (**hematogenous** dissemination) to the **lungs, bone, & liver**.

- **Regional nodal metastases are uncommon**.

- One-half of patients with **widely invasive** carcinomas succumb **die** within 10 years,

- <10% of patients with **minimally invasive** follicular carcinomas **die** within the same period.

3.Anaplastic Carcinoma

- Anaplastic carcinomas are **undifferentiated tumors** of the thyroid follicular epithelium, accounting for less than 5%of thyroid tumors.
- They are **aggressive**, with a **mortality rate approaching 100%**
- Patients are older than those with other types of thyroid cancer, with a mean age of **65 years**.

Morphology

- Anaplastic carcinomas manifest as **bulky masses** that **grow rapidly** beyond the thyroid capsule **into adjacent neck structures**.
- On microscopic examination, these neoplasms are composed of highly anaplastic cells, which may be **large & pleomorphic.**

Clinical Features

- Anaplastic carcinomas have **poor prognosis** despite therapy.
- Metastases to distant sites are **common**, but in most cases **death occurs in <1 year** as a result of aggressive local growth & compromise of vital structures.

4. Medullary Carcinoma

- Are **neuroendocrine tumors** derived from the **parafollicular cells, or C cells**, of the thyroid.
- Like normal C cells, medullary carcinomas **secrete calcitonin**, measurement of which plays an important role in the diagnosis & postoperative follow-up of patients.
- They arise **sporadically** in about 70% of cases.
- The remaining 30% are **familial**, occurring:

A. in the setting of **multiple endocrine neoplasia (MEN) syndrome 2A or 2B**,
B. or familial medullary thyroid carcinoma **without an associated MEN syndrome**,

- **Sporadic** medullary carcinomas, & **familial** cases **without** an associated MEN syndrome, occur in **adults**,.
- Cases associated with MEN-2A or MEN-2B occur in younger patients, including children.
- Morphology:
- Medullary carcinomas may arise as a **solitary** nodule or **multiple** lesions involving both lobes of the thyroid.
- **Multicentricity** is common in **familial** cases.
- Calcitonin is readily demonstrable both within the cytoplasm of the tumor cells and in the stroma
- Clinical Features:
- Medullary carcinoma manifests as a **mass in the neck**, sometimes associated with compression effects such as **dysphagia** or **hoarseness**.
- In some instances the initial manifestations are caused by the secretion of a **peptide hormone** (e.g., diarrhea caused by the secretion of vasoactive intestinal peptide).
- Screening of the patient's relatives for elevated calcitonin levels and or RET mutations permits early detection of tumors in familial cases.
- All members of **MEN-2** kindreds carrying **RET mutations** are offered **prophylactic thyroidectomies** to preempt the development of medullary carcinomas;

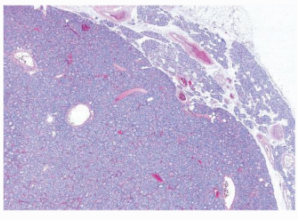
Parathyroid diseases:

I.HYPERPARATHYROIDISM

- Hyperparathyroidism may occur
a. **Primary** form b. **Secondary** Form, c. Less commonly, as **tertiary** Form.
- The first condition represents an **autonomous, spontaneous** overproduction of PTH
-The latter 2 conditions typically occur as **secondary phenomena in patients with** chronic renal insufficiency

Primary Hyperparathyroidism

- Is a common endocrine disorder & an important cause of **hypercalcemia**.
- There was a dramatic increase in the detection of cases mainly due to **routine performance of serum calcium assays in hospitalized patients**.
- The frequency of **occurrence of the various parathyroid lesions** underlying primary hyperparathyroidism.



1. Adenoma 85% to 95%
2. Primary hyperplasia (diffuse or nodular) 5% to 10%
3. Parathyroid carcinoma 1%

MORPHOLOGY

- The morphologic changes in primary hyperparathyroidism include:
1. Those **in** the parathyroid glands
2. In **other** organs affected by hypercalcemia.

- In 85-95% of cases, **one** of the parathyroid glands harbors a **solitary** adenoma.

Parathyroid adenoma:

a. Is a **well-circumscribed.**
b. **Soft, tan** أسمر nodule.
c. Invested by a **delicate capsule**.
d. Parathyroid adenomas are **confined** محصور **to a single gland.**
e. The other glands are normal in size or somewhat shrunken, as a result of feedback inhibition by elevated serum calcium.
f. Most parathyroid adenomas weigh between **0.5 and 5 g**.

- On microscopic examination:

a. Parathyroid adenomas are **composed predominantly of chief cells.**
b. A **rim of compressed, non-neoplastic parathyroid tissue,** generally separated by a fibrous **capsule**, often is visible at the edge of the adenoma.
c. **Mitotic figures are rare**.
d. In contrast with the normal parathyroid parenchyma, **adipose tissue is inconspicuous** غير واضح within adenomas.

Parathyroid hyperplasia

- Is typically a **multiglandular** process.
- In some cases, enlargement may be **grossly apparent in only one or two glands**, complicating the distinction between hyperplasia & adenoma.

Parathyroid carcinomas

- May be **circumscribed** lesions that are **difficult to distinguish from adenomas,**
- **Or** they may be **clearly invasive** neoplasms.
- These tumors enlarge **one** parathyroid gland.
- Sometimes **exceed 10 g** in weight.
- The tumor mass is usually **enclosed by a dense, fibrous capsule**.
- The diagnosis is not based on cytologic detail unreliable.

Note:

- **Invasion** of surrounding tissues & **metastasis** are the only definitive criteria.
- **Local recurrence** occurs in one third of cases, & **more distant dissemination** occurs in another one third.

Morphologic changes in other organs:

I. Skeletal changes

1. **Ostitis fibrosa cystica**

- **High PTH ⬆️ osteoclastic activity**, which results in **erosion of bone & mobilization of calcium salts**, affecting the metaphyses of long bones.

-Bone resorption is accompanied by ⬆️ osteoblastic activity & formation of new bone

- In more **severe** cases, the cortex is grossly **thinned** & the bone marrow contains increased amounts of **fibrous tissue** accompanied by foci of **hemorrhage & cysts**.

2. **Brown tumors** of hyperparathyroidism

- **Aggregates of osteoclasts**, **reactive giant cells**, & **hemorrhagic debris** form masses that **may be mistaken for neoplasms**.

II. Renal changes.

1.Nephrolithiasis: PTH-induced hypercalcemia favors formation of **urinary tract stones** calcium contain stones

2. Nephrocalcinosis: **Calcification** of the renal interstitium & tubules

III .Metastatic calcification

- Calcication **secondary to hypercalcemia** also may be seen in other sites, including the **stomach, lungs, myocardium, & blood vessels**.

- Clinical Features:

- **Primary** hyperparathyroidism usually affects **adults**
- Is much more common in **women** than in men
- The most common manifestation is an **increase in serum calcium**
- Primary hyperparathyroidism is the most common cause of clinically **silent hypercalcemia**.
- The most common cause of clinically apparent hypercalcemia in adults is **cancer**, which can cause hypercalcemia through a variety of mechanisms, including:

a. **secretion of PTH-like polypeptides** from cancers of other organs, such as lung adenocarcinoma and this is Called **paraneoplastic syndrome.**

b. **osteolytic bone metastases.**

Other laboratory findings

a. **hypophosphatemia**

b. ⬆️ **urinary excretion of Calcium & phosphate.**

Clinical Manifestations

• Pain, secondary to:
a. **fractures** of bones weakened by osteoporosis or ostitis fibrosa cystica.
b. and resulting from **renal stones** was at one time a prominent manifestation of primary hyperparathyroidism.

NOTE:

- Because serum calcium is now routinely assessed in most patients who need blood tests for unrelated conditions hyperparathyroidism is usually detected early in its course
- Additional signs & symptoms that may be encountered in some cases include:

1. GI disturbances, including constipation, nausea, peptic ulcers, pancreatitis, & gallstones.
2. CNS alterations, including depression, lethargy, & seizures.
3. Neuromuscular abnormalities, including weakness & hypotonia.
4. Polyuria & secondary polydipsia.

Secondary Hyperparathyroidism

- Secondary hyperparathyroidism is caused by **chronic depression of serum calcium levels** most often as a result of renal failure leading to compensatory overactivity of the parathyroids.
- The mechanisms by which chronic renal failure induces secondary hyperparathyroidism are complex

1. **Chronic renal insufficiency** is associated with ⬇️ phosphate excretion, which results in hyperphosphatemia.

- The elevated serum phosphate levels directly **depress serum calcium levels**.

2. **Loss of renal α1-hydroxylase activity**, which is required for the synthesis of the active form of vitamin D, **reduces the intestinal absorption of calcium**

- These alterations cause **chronic hypocalcemia**, which stimulates the activity of the parathyroid glands

2.HYPOPARATHYROIDISM

- Is less common than hyperparathyroidism.

The major causes include the following:

1. **Surgical ablation**: The most common cause is inadvertent removal of parathyroids during thyroidectomy or other surgical neck dissections.
2. **Congenital absence**: This occurs in conjunction with thymic aplasia (Di George syndrome) & cardiac defects, secondary to deletions on **chromosome 22**.

3. Autoimmune hypoparathyroidism:

- This is a hereditary polyglandular deficiency syndrome arising from **autoantibodies** to multiple endocrine organs (parathyroid, thyroid, adrenals, & pancreas).
- This condition is caused by mutations in the autoimmune regulator gene AIRE.

Lec6: Diabetes Mellitus:

Exocrine pancreas= glands & ducts that secrete enzymes, mainly for digestion.
Endocrine pancreas= Islets of Langerhans (clusters of endocrine cells), secrete hormones. There are around 1 million Islets in the pancreas!
• Islets of Langerhans contain several types of cells, the most important are alpha and beta
• Alpha cells secrete glucagon
• Beta cells secrete insulin
• Delta cells secrete somatostatin, which suppresses both insulin and glucagon.
• DM IS A GROUP OF METABOLIC DISORDERS SHARING HYPERGLYCEMIA.
• Blood glucose levels normally are maintained in a very narrow range, usually 70 to 120 mg/dL.
• This is maintained by the balance between insulin & glucagon

Insulin effects

• Increase uptake of glucose by striated muscle & adipocytes.
• Insulin has anabolic effect on lipid, protein & glycogen.
• Insulin reduces production of glucose from liver.

- Criteria to diagnose DM:

• According to the American Diabetes Association (ADA) & the (WHO), **diagnostic criteria for diabetes** include the following:
1. A fasting plasma glucose greater than or equal to 126 mg/dL, &/or
2. A random plasma glucose greater than or equal to 200 mg/dL (in a patient with classic hyperglycaemic signs &/or
3. A 2-hour plasma glucose greater than or equal to 200 mg/dL during an oral glucose tolerance test with a loading dose of 75 gm, &/or
4. A glycated haemoglobin (HbA1C) level greater than or equal to 6.5%

- PREDIABETES:

- impaired glucose tolerance.
- elevated blood sugar that does not reach the criteria for diagnosis of diabetes
-persons with prediabetes have an elevated risk for development of **frank diabetes**.

Criteria to diagnose prediabetes

• Impaired glucose tolerance (prediabetes) is defined as
1. A fasting plasma glucose between 100 and 125 mg/dL , and/or
2. A 2-hour plasma glucose between 140 and 199 mg/dL during an oral glucose tolerance test, and/or
3. HbA1C level between 5.7 & 6.4 %
• Up to one-fourth of individuals with impaired glucose tolerance will develop diabetes in the next 5 years.
NOTE Many acute stresses, such as severe infections, burns, or trauma, can lead to **transient hyperglycemia** due to secretion of hormones like catecholamine & cortisol that oppose insulin action.
-The diagnosis of diabetes requires persistence of hyperglycemia following resolution of the acute stress.

- Classification of DM:

• Type 1… absolute insulin deficiency due to *destruction* of the islets by autoimmune mechanisms
• Type 2.. Relative insulin deficiency …. Peripheral *resistance* to insulin & inadequate compensatory response of insulin secretion.

• Other rare causes:

1) **Genetic defects of beta cell function**:
- maturity onset diabetes of the young = **MODY** due to several mutations.
- insulin gene mutations.
- defects in proinsulin conversion
2) **Genetic defects in insulin action:** Insulin receptor mutations.
3) **Gestational diabetes**: During pregnancy
4) **exocrine pancreatic defects**: chronic pancreatitis, pancreatectomy, neoplasia, ..etc
5) **endocrinopathies**: Acromegaly, Cushing syndrome, pheochromocytoma
6) **infections**: CMV, coxsackievirus B, congenital rubella.
7) **drugs**: steroids

TYPE 1 Diabetes :-

- It accounts for 10% of all cases .
- Is an autoimmune disease destructing Pancreatic B cells leading to an absolute deficiency of insulin
- Most commonly develops in childhood, becomes manifest at puberty, & patients depend on exogenous insulin for survival; without insulin they develop complications
- The classic manifestations of the disease occur **late** in its course, **after 90% of the beta cells have been destroyed**.
- genetic predisposition.
- Pathogenesis:-
- Autoimmune disease
- The main immune abnormality is failure of self tolerance in T-cells specific for beta cells antigens, this failure results from combination of:

A. **Defective clonal deletion** of self reactive T-cells in the thymus.

b. **Abnormalities of regulatory T-lymphocytes** that normally dampen تخمد effector-T-cell responses

- Therefore this will lead to production of **autoantibodies against B cell antigens**, including insulin & glutamic acid decarboxylase enzyme, are detected in the blood of 70% to 80% of patients.

??? Effects of viral infections.

Type 2 diabetes:

Accounts for 80% to 90% of cases of Diabetes mellitus

- Caused by a combination of:

a. Peripheral **resistance** to insulin action

b. B-cell **dysfunction**

- B-cell dysfunction is manifested as inadequate insulin secretion in the face of insulin resistance & hyperglycemia.

Insulin resistance:

- Is defined as the failure of target tissues to respond normally to insulin
- It leads to **decreased uptake of glucose in muscle, reduced glycolysis in the liver.**
- The **liver, skeletal muscles & adipose tissue** are the major tissues where insulin resistance manifests as follows:

a. failure to inhibit gluconeogenesis in the liver which contributes to **high fasting blood glucose** levels.

b. Abnormally low glucose uptake & glycogen synthesis in the skeletal muscle following a meal, which contributes to **high postprandial blood glucose** level.

c. Failure to inhibit hormone-sensitive lipase in adipose tissue leading to **excess circulating free fatty acids**.

Obesity & Insulin Resistance :

- **Visceral obesity** is common in majority of affected patients with type 2 DM
- and **insulin resistance is present even with simple obesity un-accompanied by hyperglycemia**, indicating a fundamental abnormality of insulin signaling in states of fatty excess.

The risk of diabetes increases as the body mass index increases, suggesting a dose-response relationship between body fat & insulin resistance.

- Metabolic syndrome is characterized by constellation of finding including:

a. Visceral **obesity**

b. Insulin **resistance**

c. Glucose **intolerance**

d. **Cardiovascular** risk factors such as hypertension & abnormal lipid profile.

- In diabetes it is not only the absolute amount but the distribution of body fat that has an effect on insulin sensitivity.
- Central obesity (abdominal fat) is more likely to be associated with insulin resistance than in peripheral fat (gluteal/subcutaneous) obesity.

A. Role of excess free fatty acids (FFAs): The level of intracellular triglycerides often is markedly **increased in muscle & liver tissues** in obese persons because excess circulating FFAs are deposited in these organs .

- Intracellular triglycerides are potent **inhibitors of insulin signaling & result in an acquired insulin resistance**.

b. Role of inflammation: mediated by **cytokines** secreted in response to excess FFAs results in **peripheral insulin resistance & beta cell dysfunction.**

- Excess FFAs within macrophages & beta cells can engage the **inflammasome**, leading to secretion of IL-1β which mediates secretion of additional cytokines from macrophages, that are released into the circulation & **act on the major sites of insulin action to promote insulin resistance.**

c. Role of adipokines:

- Adipose tissue is not just a passive storage tissue for fat
- It is also an endocrine organ that **releases hormones in response to changes in the metabolic status**
- A variety of proteins secreted into the systemic circulation by adipose tissue
- and these molecules are called **adipokines or adipose cytokines** & some of them cause *hyperglycemia* & others such as leptin & adiponectin *decrease blood glucose* by increasing insulin sensitivity in peripheral tissue
- **Adiponectin is decreased in obesity** therefore leading to insulin resistance.

Beta cell dysfunction:

• Inability of beta cells to meet the increased demand on insulin due to peripheral resistance.
• Cause: multifactorial & overlap with those related to **peripheral resistance**.
• Examples: -**FFAs cause cytokine release** from the pancreatic Islets causing **inflammatory damage**.
-**Amylin** is secreted by the β- cells & its abnormal aggregation results in **amyloid** that replaces the islets.

MORPHOLOGY of DM : Pancreas

a. Reduction in the number & size of islets, most often in **type 1** particularly with rapidly advancing disease.
b. Leukocytic infiltration of the islets: seen in both **type 1 & type 2** DM although it is more severe in type 1.
- In both types inflammation is often absent by the time the disease is clinically evident.
c. Amyloid replacement of islets in long-standing **type 2** diabetes, appear as deposition of **pink, amorphous material beginning in capillaries between cells.**
d. fibrosis of the islets At advanced stages.

- clinical features:

a. The **hyperglycemia exceeds the renal threshold forwater reabsorption**, & **glycosuria induces an osmotic diuresis & *polyuria***,
b. The obligatory renal water loss combined with the hyperosmolarity tends to deplete intracellular water, triggering the thirst centers of the brain & this generates **intense thirst (*polydipsia*)**.
c. Deficiency of insulin leads to **catabolism of proteins & fats** which tends to induce a **negative energy balance**, which in turn leads to **increasing appetite (*polyphagia*)** .

- Acute complications of DM:

- In patients with type 1 diabetes, unusual physical activity, infection or any other form of stress worsen the metabolic imbalance leading to diabetic **ketoacidosis**

Pathogenesis:

- The **plasma glucose is in the range of 500 to 700 mg/dl** because of absolute deficiency of insulin & unopposed effects of counterregulatory hormones (epinephrine & glucagon)
- The marked hyperglycemia causes osmotic diuresis & dehydration.

Activation of ketogenic machinery

- Insulin deficiency leads to activation of hormonesensitive lipase with resultant excessive break down of adipose tissue giving rise to increase of FFAs which are oxidized in the liver to produce ketones

• **Ketogenesis is an adaptive phenomenon in times of starvation** generating ketones as a source of energy for consumption by vital organs (brain)

• **The rate of which ketones are formed may exceed the rate at which ketones they can be used by peripheral tissues ➡️ ketonemia & ketonuria.**

• If the urinary excretion of ketones is compromised by dehydration, the accumulating **ketones decrease blood PH resulting in metabolic acidosis**.

- Long term complications of DM:

• Blood vessels: atherosclerosis, hyaline arteriosclerosis, microangiopathy.

• Nephropathy: Glomerular lesions, arteriosclerosis, pyelonephritis.

• Ocular complications

• neuropathy

Morphology & clinical manifesations of complications

1. Diabetic Macrovascular Disease:

- The hallmark is **accelerated atherosclerosis affecting the aorta**, large & medium-sized arteries & it is more severe with early onset in diabetics than in nondiabetics

- **Myocardial infarction** due to Coronary artery atherosclerosis is the **most common cause of death in diabetics** and is as common in diabetic women as in diabetic men

- **Gangrene** of the lower extremities is 100 times more common in diabetics than in the general population ..

2. Hyaline arteriolosclerosis,

- Is the vascular lesion associated with **hypertension**

- Is both more prevalent & more severe in diabetics than in nondiabetics, but it is **not specific for diabetes** & may be seen in elderly persons who do not suffer from either diabetes or hypertension.

- It takes the form of hyaline thickening of the wall of the arterioles, which causes **narrowing of the lumen.**

- In diabetic patients, its severity is related not only to the **duration** of the disease but also to the presence or absence of **hypertension**.

3. Diabetic Microangiopathy:

Diffuse **thickening of basement membranes**, is most evident in the capillaries of the **skin, skeletal muscle, retina, & renal glomeruli**.

- It may be seen in **renal tubules, nerves, & placenta**.

- It underlies the development of **diabetic nephropathy, retinopathy, & some forms of neuropathy.**

4. Diabetic Nephropathy:

- The kidneys are prime targets of diabetes & renal failure is second only to **myocardial infarction** as a cause of death from this disease lesions encountered are:

A. Glomerular lesions, several forms of glomerulonephritis occur.

B. Renal atherosclerosis and arteriolosclerosis.

C. Pyelonephritis: inflammation in the interstitial tissue & involve the tubules & it has both acute & chronic forms

Clinical manifestations of diabetic nephropathy

- Is a leading cause of end stage renal disease in the US.

- The earliest manifestation of diabetic nephropathy is the appearance of **small amounts albumin in the urine** (more than 30 & less than 300 mg/day) called **microalbuminuria.**

- Without specific interventions, approximately 80% of patients with type 1 DM and 20-40% of patients with type 2 DM will develop **overt nephropathy with macroalbuminuria** excretion of more than 300 mg/day over 10 to 20 years, usually accompanied by **hypertension**.

- By 20 years after diagnosis, >75% of patients with type 1 diabetes & 20% of patients with type 2 DM with overt nephropathy will develop **end stage renal disease** necessiating dialysis or renal transplantation

5. Ocular Complications of Diabetes:

- **Visual impairment, & blindness**, is one of the more feared consequences of long-standing DM.
- **Retinopathy**, the most common pattern, consists of changes that are considered by many ophthalmologists to be virtually diagnostic of the disease.
- DM currently is the fourth leading cause of acquired blindness in the United States.
- About 60% to 80% of patients develop a form of diabetic retinopathy approximately 15 to 20 years after diagnosis.
- diabetic patients also have an increased propensity for **glaucoma & cataract** formation.

6. Diabetic Neuropathy:

a. The most frequent pattern of involvement is that of a **bilateral peripheral, symmetric neuropathy of the lower extremities affecting motor & sensory nerves mainly sensory**

b. Autonomic neuropathy produces **disturbances in bowel & bladder function** & sometimes **sexual impotence.**

C. Mononeuropathy, which may manifest as **sudden foot drop or wrist-drop or isolated cranial nerve palsies**

- The neurologic changes may be the result of **microangiopathy** & increased permeability of capillaries that supply the nerves, as well as **direct axonal damage**

- Glycemic control:

- Glycemic control is assessed clinically by **measuring the percentage of glycosylated hemoglobin known as HbA1C** which is formed by nonenzymatic addition of glucose to hemoglobin in red blood cells
- Unlike blood glucose levels, **HbA1C is a measure of glycemic control over long period of time** (2-3 months) **unaffected by day to day variation**
- The recommendation is to maintain HbA1C at less than 7% to reduce the risk for long term complications.

لما ن مساحة للتعبير عن الرأي ..

Adrenal gland Pathology الغدة الكظرية/ الغدة فوق الكلوية:

• The adrenal glands are paired endocrine organs consisting of two regions, the cortex and medulla, which differ in their development, structure, and function.
• The cortex consists of 3 layers of distinct cell types: zona glumerulosa, fasiculata, reticularis.

The adrenal cortex synthesizes three different types of steroids:

• **glucocorticoids** (principally cortisol), synthesized primarily in the zona fasciculata, with a small contribution from the zona reticularis
• **Mineralocorticoids**, the most important being aldosterone,secreted from zona glomerulosa
• **Sex steroids** (estrogens & androgens), produced largely in the zona reticularis

Adrenal medulla

• The adrenal medulla is composed of chromaffin cells, which synthesize & secrete catecholamines, mainly epinephrine.

Adrenal cortex: same old story: mass effect and hormonal abnormalities.

• **Hyperadrenalism** :
*Hypercortisolism *hyperaldosteronism *adrenogenital syndromes (won't be discussed)
• **Hypoadrenalism**:
*acute adrenal insufficiency
*chronic adrenal insufficiency (Addison disease)
*secondary adrenal insufficiency.
• **Masses = Neoplasms**
* adenoma *carcinoma

Hypercortisolism (Cushing Syndrome)

- **Exogenous**: if you treat patients with glucocorticoids (Iatrogenic): this is **the most common cause of Cushing syndrome**.
- **Endogenous** causes:
A. **Hypothalamic-pituitary diseases causing hypersecretion of ACTH (Cushing disease).**
B. Primary **adrenal** hyperplasia & neoplasms.
C. Secretion of **ectopic** ACTH by nonpituitary tumors.

Iatrogenic Cushing: effect on the adrenals

• In patients in whom the syndrome results from exogenous glucocorticoids, suppression of endogenous ACTH results in bilateral cortical **atrophy**, due to a lack of stimulation of the zona fasciculata & zona reticularis by ACTH.

- HYPOTHALAMIC- PITUITARY CAUSES CUSHING DISEASE:

-70% of cases of spontaneous, endogenous Cushing syndrome are due to **Cushing disease**.
- Occurs most frequently during young adulthood (the 20s & 30s)
- mainly affecting **women**.

- CUSHING DISEASE:

-majority of cases are due **to pituitary ACTH-producing adenoma.**
- In the remaining patients, the anterior pituitary contains areas of *corticotroph cell hyperplasia* which may be: primary or, less commonly, secondary to CRH producing tumor

- Diffuse hyperplasia:

• Diffuse hyperplasia is **found in patients with** ACTH-dependent Cushing syndrome.
• **Both glands are enlarged**, either subtly or markedly, each weighing up to **30** g.
• The yellow colour of diffusely hyperplastic glands derives from the presence of **lipid-rich cells**, which appear **vacuolated** under the microscope.

- PRIMARY ADRENAL HYPERPLASIA & NEOPLASMS:

- 10% to 20% of cases of endogenous Cushing syndrome are due to primary diseases in the adrenal gland.
- This is called *ACTH-independent Cushing syndrome*, because of the **low serum ACTH.**
- It is caused by **adrenal adenoma or carcinoma**.
- Can also be caused by **primary hyperplasia** but this is very rare.

- Primary adrenal hyperplasia:

• In primary cortical hyperplasia, the cortex is replaced almost entirely by **macronodules** or 1- to 3-mm **micronodules**.

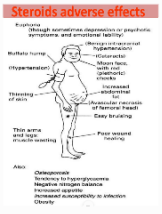
- ECTOPIC ACTH BY NONPITUITARY TUMORS:

- mostly caused *by small cell carcinoma of the lung.*
- The adrenal glands undergo bilateral hyperplasia due to elevated ACTH.

- Primary adrenocortical neoplasms:

- Are more common in women in their 30s to 50s.
a. Adrenocortical adenomas=yellow tumors surrounded by ***thin capsules***, most weigh <30 g.
b. Carcinomas tend to be ***nonencapsulated*** masses, exceeding 200 - 300 g in weight,

- CLINICAL MANIFESTATIONS OF CUSHING SYNDROME:



a. Hypertension & weight gain.
b. truncal obesity, "moon facies," accumulation of fat in the posterior neck & back ("buffalo hump") .
c. Glucocorticoids induce gluconeogenesis, thus hyperglycemia, glucosuria, & polydipsia.
d. The catabolic effects on proteins cause loss of collagen & resorption of bone which results in osteoporosis & susceptibility to fractures.
e.The skin is thin, fragile, & easily bruised; cutaneous striae are particularly common in the abdominal area
f. Patients are at increased risk for a variety of infections.
g. Hirsutism & menstrual abnormalities.
h. Mental disturbances, mood swings, depression, psychosis.

aldosterone:

• The **renin–angiotensin–aldosterone system (RAAS)** is a hormone system that is involved in the regulation of the plasma sodium concentration & arterial blood pressure.

- HYPERALDOSTERONISM:

Primary hyperaldosteronism:

- autonomous overproduction of aldosterone + secondary suppression of renin-angiotensin system + decreased plasma renin activity.

Secondary hyperaldosteronism:

- Secondary to activation of renin-angiotensin system characterized by increased levels of plasma renin.

- CAUSES OF SECONDARY HYPERALDOSTERONISM:

a. Decreased renal perfusion (renal artery stenosis)
b. Arterial hypovolemia & edema e.g heart failure
c. Pregnancy (caused by **estrogen-induced increases** in plasma renin substrate)

- PRIMARY HYPERALDOSTERONISM:

a. Bilateral idiopathic hyperaldosteronism,
- bilateral nodular hyperplasia of adrenals
- the most common underlying cause (60% of cases)

b. Adrenocortical neoplasm, adenoma (the most common cause) or, rarely, an adrenocortical carcinoma.
- In approximately 35% of cases, the cause is a solitary aldosteronesecreting Aldosterone-producing adrenocortical adenoma referred to as **Conn syndrome**

c. Rarely, familial hyperaldosteronism may result from a genetic defect that leads to overactivity of the aldosterone synthase gene, CYP11B2.

- Features of aldosterone producing adrenocortical adenoma:

• Solitary • Encapsulated • Well circumscribed
• Histology: can show endocrine atypia
• May contain **spironolactone bodies if treated with spironolactone.**

- Spironolactone bodies:

• Aldosterone producing adenomas contain eosinophilic, laminated cytoplasmic inclusions= spironolactone bodies which appear after treatment with spironolactone (an aldosterone antagonist)

- CLINICAL FEATURES OF HYPERALDOSTERONISM:

The clinical hallmark is ***hypertension.***
- Hyperaldosteronism may be the most common cause of secondary hypertension
- ***Hypokalemia.***

- Adrenal insufficiency:

• Decreased hormonal production from the adrenal
• Divided into 3 types:
1. **Acute** insufficiency 2. **Chronic** insufficiency = Addison disease 3. **Secondary** insufficiency

1- Acute Adrenocortical Insufficiency:

- Occurs in the following situations:
a. Crisis in patients with chronic adrenocortical insufficiency precipitated by stress
b. In patients maintained on exogenous corticosteroids .. Sudden withdrawal, or stress
c. Massive adrenal hemorrhage

3.Massive adrenal hemorrhage

May destroy enough of the adrenal cortex to cause acute adrenocortical insufficiency.
- This condition may occur :
1. In patients maintained on anticoagulant therapy
2. Patients suffering from sepsis : a condition known as the Waterhouse-Friderichsen syndrome

- Sepsis due to: Neisseria meningitidis ,Pseudomonas spp., , and Haemophilus influenzae
- Underlying cause involves endotoxin-induced vascular injury

2- primary chronic adrenocortical insufficiency (Addison disease):

- Uncommon disorder resulting from **progressive destruction** of the adrenal cortex.
- Causes: Autoimmune adrenalitis - Infections - Metastatic tumors

- ADDISON DISEASE:

- Causes:

1. Autoimmune adrenalitis

- 60% to 70% of Addison disease cases and is the most common cause of primary adrenal insufficiency in developed countries.
- There is autoimmune destruction of steroid-producing cells, and **autoantibodies to several key steroidogenic enzymes** have been detected in affected patients

2. Infections: Tuberculosis & Fungal infections

- **Tuberculous adrenalitis**, which once accounted for as many as 90% of cases of Addison disease, has become less common with the advent of anti-tuberculosis therapy.
- Disseminated infections caused by **Histoplasma capsulatum** & **Coccidioides immitis**.
- Patients with **AIDS** are at risk for the development of adrenal insufficiency from several infectious (cytomegalovirus and TB) and noninfectious.

3. Metastatic neoplasms involving the adrenals:

Carcinomas of the lung & breast are the most common primary sources.

3- Secondary adrenocortical insufficiency:

Hypothalamic-pituitary diseases including:

• Metastasis • Infection • Infarction • Irradiation • Can be part of pan hypopituitarism.

- Clinical features of adrenal insufficiency:

- Clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the adrenal cortex has been compromised.

a. progressive weakness & easy fatigability .

b. GI disturbances are common & include anorexia, nausea, vomiting, weight loss, & diarrhea

c. In patients with primary adrenal disease, increased levels of ACTH precursor hormone stimulate melanocytes, with resultant hyperpigmentation of the skin & mucosal surfaces: The face, axillae, nipples, areolae, & perineum are mainly affected.

Note: hyperpigmentation is not seen in patients with secondary adrenocortical insufficiency.

d. Decreased aldosterone in primary hypoadrenalism results in potassium retention & sodium loss, with consequent:

- hyperkalemia, hyponatremia, volume depletion, & hypotension,
- In secondary hypoadrenalism is characterized by deficient cortisol & androgen output but normal or near-normal aldosterone synthesis. This is because **ACTH doesn't affects the production of aldosterone**.

- Adrenal medulla:

• Chromaffin cells are derived from the neural crest, they Secrete catecholamines.
• Most important disease: neoplasms.

- TUMORS OF THE ADRENAL MEDULLA:

- Pheochromocytoma:

- gives rise to a surgically correctable form of hypertension.
- Pheochromocytomas usually subscribe to "**rule of 10s**":

a. *10% of pheochromocytomas are extraadrenal, called **paragangliomas***,
b. *10% of adrenal pheochromocytomas are bilateral*; this proportion may rise to 50% in cases that are associated with familial syndromes.
c. *10% of adrenal pheochromocytomas are malignant*,
d. 10% familial.. Now we think up to 25% might be familial.

- Microscopically:

- Are composed of polygonal to spindle-shaped chromaffin cells & their supporting cells, compartmentalized into small nests, or **Zellballen**, by a rich vascular network.
- The cytoplasm has a finely granular appearance, because of the presence of granules containing catecholamines.
- The nuclei of the neoplastic cells are often **pleomorphic**.
- The definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of **metastases**.

- Clinical Features:

- The predominant clinical manifestation is **hypertension**.
- **Sudden cardiac death** may occur, probably secondary to catecholamine-induced myocardial irritability & ventricular arrhythmias.

"وما عند الله خير وأبقى"